UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

DATE: JUNE 16, 1999

MEMORANDUM

SUBJECT: **METHAMIDOPHOS:** Review of Two Generation Reproduction Toxicity Study in Rats (MRID No.4466001 and Addenda (MRID No. 44815401 and 44815402)/Impact on Dietary and Non-dietary Risk Assessments

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February 3, 2000

Registrant: Bayer
Chemical: Methamidophos
DP Barcode: D245195, D256022 PC Code: 101201

ACTION: Review the two-generation reproduction toxicology study and determine the impact on dietary and non-dietary risk assessments.

SUMMARY: On January 20, 1998, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) evaluated the data base on Methamidophos to re-assess the Reference Dose (RfD) and to determine the Uncertainty Factor and/or Margin of Exposure for dietary and non-dietary exposure risk assessments (see HED document No. 012921). The Committee also addressed the potential sensitivity of infants and children as required by the Food Quality Protection Act (FQPA) of 1996. Since that meeting, the Registrant has submitted a two-generation reproduction toxicology study in rats (MRID No. 44466001) along with two addenda to the Final Report (MRID Nos. 44815401 and 44815402).

Presented below are the Citation and Executive Summary for the reviewed study (MRID No. 44466001); the Data Evaluation Report is attached. The findings of this study in conjunction with the supplemental information submitted by the registrant are acceptable and satisfy the guideline requirement for a two-generation reproduction study in the rat.

CITATION: Eigenberg, D.A. and Freshwater, K.J. (1998) A Two-Generation Dietary Reproduction Study in Rats Using Technical Methamidophos. Bayer Corporation, Agricultural Division, 17745 South Metcalf, Stilwell, KS 66085-9104. Study Number 95-672-GJ. January 5, 1998. MRID 44466001. Unpublished

Astroff, A.B. and Eigenberg, D.A. (1998) Supplemental Submission to a Two-Generation Dietary Reproduction Study in Rats Using Technical Methamidophos. Bayer Corporation, Agricultural Division, Toxicology, 17745 South Metcalf, Stilwell, KS 66085-91401. Addendum to Study Number 95-672-GJ. October 9, 1998. MRID 44815401. Unpublished

Moore, K.D. (1999) Supplemental Submission to a Two-Generation Reproduction Study in Rats with Technical Grade Methamidophos (MONITOR®). Bayer Corporation, Agricultural Division, Toxicology, 17745 South Metcalf, Stilwell, KS 66085-91401. Addendum to Study Number 95-672-GJ. February 23, 1999. MRID 44815402. Unpublished

EXECUTIVE SUMMARY: In a 2-generation reproduction study (MRID Nos. 44466001, 44815401 and 44815402), Methamidophos technical, only 73% a.i., was administered to 30 Sprague-Dawley rats/sex/dose in the diet at dose levels of 0, 1, 10 and 30 ppm. However, based upon actual mean analyses of the dose preparations and correction for % a.i., dose levels would be equivalent to 0, 0.73, 7.14, and 19.06 ppm. These corrected dose levels appear more realistic since they take into account both mean analytical determinations as well as the relatively low levels of active ingredient (the percent of active ingredient was intentionally maintained at such a low level due to the hygroscopic nature of the active ingredient, Methamidophos). During the premating growth period, corrected dose levels of Methamidophos were 0, 0.08, 0.66, and 1.76 mg/kg/day. However, during

the lactation period corrected dose levels were 0, 0.15, 1.10, and 2.85 mg/kg/day reflecting the highest dose levels during the study. In this reproduction study, plasma, RBC, and brain cholinesterase inhibition were also assessed in adult and weanling rats.

During the growth phase, mean body weights of F1 adult males were reduced in both the 10 and 30 ppm dose levels. Food consumption was also consistently increased in P and F1 males over the majority of weeks sampled. Terminal body weights were statistically reduced in 30 ppm P males and 10 and 30 ppm F1 males. Cholinesterase inhibition was evident at all dose levels. These findings included statistically significant RBC inhibition in the 1 ppm P males which reflected greater than a 20% inhibition as compared to control values, statistically reduced RBC cholinesterase in F1 males, and significantly reduced brain cholinesterase in P and F1 females at 1 ppm, the lowest dose tested. **Based on RBC and brain cholinesterase inhibition at the LDT of 1 ppm, a NOEL for parental systemic toxicity was not determined in this study. The NOAEL is <1 ppm [<0.73 ppm (0.08 mg/kg/day) if corrected for actual analytical concentration and percent a.i.].**

Methamidophos administration was associated with significantly reduced pup weights at the 1 ppm, 10 ppm, and 30 ppm dose levels during the F1a lactation period, in the 10 ppm and 30 ppm levels in the F1b and F2b lactation periods, and in the 30 ppm level in the F2a lactation period. Additionally, plasma, RBC and brain cholinesterase were significantly reduced at the 30 ppm dose level in pups on postnatal day 4 and at the 10 and 30 ppm dose levels in weanling pups (postnatal day 21). Also, the number of stillborn pups was increased at the 30 ppm level, and pup survival throughout lactation was decreased at this dose level. This is further demonstrated by a decrease in the lactation index during the F1a, F1b, and F2b matings at the high dose. The number of pups cannibalized at the 30 ppm level was also significantly increased. **Based on pup body weight decrements at the LDT of 1 ppm, it is concluded that no NOEL for offspring toxicity was determined in this study. This study is considered acceptable based on the finding that the effects observed in the offspring at the low dose level appear to be a threshold effect. The NOAEL is <1 ppm [<0.73 ppm (0.08 mg/kg/day) if corrected for actual analytical concentration and percent a.i.].**

This reproduction study in the rat is classified as **acceptable.** This study satisfies the guideline requirement for a two-generation reproduction study (OPPTS 870.3800, §83-4) in the rat, although no NOAEL's for parental and offspring toxicity were determined in this study. While the effects relative to cholinesterase inhibition in parental animals are clearly apparent at all dose levels, the fact that there is no NOAEL for a parental effect is not a requirement relative to acceptability of the study for regulatory purposes since the primary purpose of the study is to investigate reproductive and offspring toxicity.

As indicated above, a NOEL for parental systemic toxicity was not established. The NOAEL is <0.08 mg/kg/day. For offspring toxicity, a NOEL was also not established, and the NOAEL is also <0.08 mg/kg/day (i.e., the LDT = 0.08 mg/kg/day; however, even this latter value is a threshold. Based on this information, the new two-generation reproduction data support the selected endpoint [i.e., brain cholinesterase inhibition (ChEI)] and the selected LOAEL (0.06 mg/kg/day) and NOAEL (0.03 mg/kg/day) for the chronic RfD as established by the HIARC in 1998, based upon an 8-week oral toxicity study in rats. The

parental systemic LOAEL of the two-generation study when adjusted for the lack of a NOAEL (3x), provides a value of 0.026 mg/kg/day, which is equivalent to the NOAEL used to calculate the RfD. In addition, the two-generation study did not provide any endpoints appropriate for the acute dietary risk assessment.

Furthermore, in the new two-generation reproduction study, no evidence of a quantitative susceptibility was observed. For the parental animals, ChEI was seen at 1 ppm (the lowest dose tested). At the same dose, threshold reductions in offspring body weight were noted. Although the highest dose tested (30 ppm, 19.06 ppm [2.85 mg/kg/day if corrected for actual analytical concentration and percent a.i.]),compromised offspring survival, this finding occurred in the presence of severe brain ChEI (up to 80% inhibition) in the parental females. Additionally, offspring mortality may have been affected by maternal behavior since the incidence of dams cannibalizing their offspring was increased at 30 ppm. It was, therefore, concluded that the study provided no unequivocal evidence of increased quantitative susceptibility to the offspring. This conclusion does not alter the previous determination of the FQPA safety factor for methamidophos (reduced to 3x) which was based upon other considerations as well (see HIARC Report). Consequently, the doses and endpoints selected for the acute and chronic dietary as well as the inhalation (any time) risk assessments by the HIARC on January 20, 1998 remain unchanged. Similarly, the doses selected for the short-term, intermediate-term and long-term dermal risk assessments remain unchanged (see HED document no. 013394).

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